REMARKS

Claim 5 has been amended to remove the informality.

As discussed below, BRL 35135 is not a In view of the comments that BRL 35135 is not a β_3-agonist it has therefore been deleted from claim 6. The typographical errors introduced into the claims in response to the restriction requirement buy use of an optically character read copy of the original have been corrected.

The only substantive issues raised in the official action are rejections under 35 USC 103. The Examiner is of the opinion that claims 3-6 and 9-12 are obvious in light of Carson (Current Problems in Cardiology) in view of Wheeldon (British Journal of Clinical Pharmacology).

The applicants make the following submissions on these rejections.

Claim 3

The Examiner notes that Carson teaches that heart failure typically begins with an initial insult impairing systolic function and over time the response to this injury ultimately leads to compromised heart function. Although the Examiner concedes that Carson does not teach administration of β_3-adrenoreceptor agonists, this is allegedly taught by Wheeldon which is said to teach the administration of therapeutic amounts of the β_3-adrenoreceptor agonist BRL 35135 which leads to increased systolic blood pressure and stroke distance (pages 364-366 of Wheeldon). Based on this, the Examiner considers that a person skilled in the art would consider claim 3 obvious in light of the combination of Carson and Wheeldon.

In reply, Applicants note that Wheeldon et al describes an apparent positive inotropic effect of BRL 35135 i.e. an increase in blood pressure and heart rate. Applicants submit that it is firmly

established that such positive inotropic agents are harmful in heart failure. Applicants submit that a person skilled, in the art would not administer a drug that increases systolic blood pressure to a patient with heart failure or myocardial hypertrophy (i,e. to counter the systolic impairment identified by the Examiner) as evidence-based treatments of those conditions known to those skilled in the art lower blood pressure. Accordingly, any drug that increases systolic blood pressure in normal people would not be considered a treatment of heart failure. Furthermore, Applicants note that this is taught in numerous standard texts including the Cecil reference the Examiner has cited in relation to claims 13 and 14 (see left-hand column on page 217 of Cecil),

Applicants contend that it is accepted by a person of skill in the art increasing systolic blood pressure with a compound such as BRL 35135 is contrary to accepted practice. Therapeutically useful treatments of heart failure such as angiotensin converting enzyme (ACE) inhibitors, β-blockers and aldosterone antagonists listed in Table 48.1 on page 218 in Cecil all lower blood pressure.

Applicants assert that BRL 35135 is <u>not</u> a β_3 agonist in humans. Agonists such as BRL 35135 were initially developed on the basis of rodent adrenoreceptors and since that time it has become appreciated that such agonists have poor selectivity for the human β_3-receptor as taught by Arch (Arch JR: beta(3)-Adrenoreceptor agonists; potential, pitfalls and progress. Eur J Pharmacol (2002) 440(2~3):99-107). Applicants submit that Wheeldon demonstrates this point clearly. The standard method for selecting β_2-adrenoreceptor activation is to measure finger tremor and Wheeldon shows that BRL 35135 induces as much finger tremor as the classical selective β_2 adrenoreceptor agonist salbutamol. In addition, this finger tremor is blocked by the β_1/β_2-adrenoreceptor antagonist nadolol but not the β_1 antagonist bisoprolol (Figure 1 of Wheeldon). Accordingly, the BRL 35135 induced increases in heart rate and systolic blood pressure which the Examiner notes were blocked by nadolol were not, in fact, β_3-adrenoreceptor mediated effects, thus BRL 35135 is not a β_3-agonist in humans.

In summary, Wheeldon teaches that BRL 35135 has effects that a person skilled in the art would consider especially harmful in heart failure and is not a β_3-adrenoreceptor agonist in humans. There is therefore no rationale based on these documents as to why one skilled in the art would wish to use any β_3 adrenoceptor agonist for treatment of an individual suffering from or susceptible to heart failure or myocardial hypertrophy. Accordingly, Applicants submit that Wheeldon has no bearing on the patentability of the claims as currently pending in this application.

Thus in light of the foregoing comments the Applicants submit that claim 3 is not obvious in light of Wheeldon and Carson.

Claim 4

The Examiner is of the opinion that any individual included in the patient population defined by claim 4 would be expected to have at least one clinical symptom of heart failure. The Examiner's rejection of claim 4 appears to be made on the same basis as the rejection of claim 3. In view of our comments above addressing the rejection of claim 3 we do not consider that further comment is required in relation to claim 4.

Claims 5 and 6

The Examiner is of the opinion that Wheeldon teaches administering BRL 35135 to a person with heart failure or myocardial hypertrophy and in view of this the Examiner has formed the opinion that Wheeldon teaches at least one of the optional components of claims 5 and 6, thus claims 5 and 6 are allegedly obvious. As per the comments above that Wheeldon teaches effects not mediated by a β_3-adrenoreceptor Applicants submit that this rejection is now moot.

Claims 7 and 8

The Examiner is of the opinion that claims 7 and 8 are obvious in light of Carson and Wheeldon and further in view of Gauthier. The Examiner concedes that the combination of Carson and Wheeldon does not teach the β_3-adrenoreceptor agonist BRL 37344 nor does that combination of references teach compositions of β_3-adrenoreceptor agonists further comprising β_1- and/or β_2~adrenoreceptor antagonist activity.

In relation to claim 7 the Examiner is of the opinion that Gauthier teaches a number of β_3-adrenoreceptor agonists including BRL 37344 (page 426 of Gauthier). Furthermore, the Examiner alleges that Gauthier teaches that BRL 37344 potently activates β_3-adrenoreceptors and only weakly interacts with β_1- and β_2-adrenoreceptors. However, the Applicants note that Gauthier states on page 430 that in the context of heart failure "specific β_3-adrenoreceptor antagonists might be more desirable." Thus, the Applicants contend that Gauthier teaches away from the invention as presently claimed.

The Examiner is also of the opinion that Gauthier teaches β_3-adrenoreceptor agonists further comprising β_1 and/or β_2-adrenoreceptor antagonist activity, for example, CGP 12177 (page 426 of Gauthier). Thus, the Examiner has concluded that Gauthier teaches claim 8 of the present application and contends that a person skilled in the art would be motivated to combine the teaching of Gauthier with that of Carson at the time the invention was made as BRL 37344 selectively activates β_3-adrenoreceptors potentially avoiding the β_2-adrenoreceptor mediated effects produced by BRl 35135 taught by Wheeldon. The Examiner goes on to note that Gauthier's disclosure of a subset of β_3 adrenoceptor agonists possessing the β_1-/β_2- adreno receptor antagonistic properties of a beta-blocker would have been an especially strong motivation to combine the teachings of the citations in order to arrive at the invention defined in claims 7 and 8 as currently pending.

The Applicants respectfully disagree with the Examiner's opinion and note Gauthier's statement on page 427, left-hand column, second full paragraph, where it is stated that "functional observations

using β_3-adrenoreceptors agonists have yielded conflicting results". The applicants also note that in the right~hand column of page 427, last paragraph, Gauthier discusses the variability of expression of β_3-receptors and notes that, as pointed out above, β_3-adrenoreceptor transcripts are not detected in rat ventricles (Arch JR (2002)). There is therefor no rational underpinning for combining these documents as is required by the Supreme Court's decision in *KSR International Co. v. Teleflex, Inc.* 550 U.S. 398 82 USPQ2d 1385 (2007) . Accordingly, the Applicants assert that on reading Gauthier, a person skilled in the art would not be motivated to combine the teachings of Carson, Wheeldon and Gauthier to arrive at the invention defined in claims 7 and 8,

In fact it is further submitted that a skilled addressee aware of Gauthiers's caution that specific β_3-adrenoreceptor antagonists might be more desirable in the treatment of heart failure or myocardial hypertrophy would bring that knowledge to a reading of either Carson or Wheeldon, thereby being further motivated away from the present invention as now claimed.

Claims 9·12

The Examiner is of the opinion that Wheeldon teaches the step of administering a β_1- or β_2-adrenoreceptor antagonist, for example the β_3 antagonist bisoprolol, and thus as Wheeldon allegedly teaches the additional step defined in claim 9, the Examiner considers that claim 9 is obvious.

Similarly, the Examiner is of the opinion that Wheeldon teaches the administration of the betablocker nadolol as defined in claim 10, and administration of bisoprolol with a β_1-adrenoreceptor selective agonist as defined in claim 11. Thus, Wheeldon allegedly teaches the administration of at least one of the optional components defined in each of claims 10 and 11, and the Examiner has formed the opinion that claims 10 and 11 are obvious.

The Examiner is also of the opinion that Wheeldon teaches the step of administration of a

betablocker (for example bisoprolol) before administration of a β_3-adrenoreceptor agonist thereby leading the Examiner to the opinion that Wheeldon teaches at least one of the optional steps of claim 12, thus that claim is obvious.

The Examiner has stated that it would be obvious to a person skilled in the art at the time the invention was made to be motivated to treat heart failure with BRL 35135 as taught by Wheeldon which allegedly teaches that BRL 35135 increases systolic pressure and cardiac output in vivo in humans.

The Examiner asserts that Wheeldon discloses β-blockers as beneficial in heart failure. To achieve treatment of myocardial hypertrophy or heart failure, the present application describes how a β_3-adrenoreceptor agonist may be administered in combination with traditional blockers of β_1- and/or β_2-receptors. The Applicants note that the claims of the present application require β_3~adrenoreceptor stimulation in the treatment of myocardial hypertrophy or heart failure. The Applicants direct the Examiner's attention to the stated aim of Wheeldon (pages 363~364) which was to "clarify further whether β_3-adrenoreceptors may mediate chronotropic (effects on heart rate) or inotropic (effects on contractility) in man using the β_3-adrenoreceptor agonist BRL 35135". For this purpose, Wheeldon administered BRL 35135 alone or in combination with the β_1 receptor antagonist bisoprolol or the combined β_1/β_2-receptor antagonist nadolol to normal young males free of heart failure. The purpose of the co-administration of nadolol and bisoprolol in Wheeldon was entirely restricted to using the β-blockers as pharmacological tools to isolate any activity of β_1 and β_2 receptors and so investigate the effects of BRL 35135.

The purpose of administering β_3-adrenoreceptor agonists in combination with β_1/β_2-receptor antagonists as described in the present application, is entirely related to the goal of achieving selective β_3-adrenoreceptor activation for a therapeutic purpose. In contrast, the combined BRL 35135/β_1/β_2-receptor antagonist administration in Wheeldon was an attempt at experimentally dissecting receptor physiology without any express or implied therapeutic purpose. In addition.

there are no therapeutic implications suggested or taught by Wheeldon.

The Applicants assert that Wheeldon, as indicated above, neither teaches nor suggests the use of β_3-adrenergic receptor agonists in the treatment of heart failure or myocardial hypertrophy. Accordingly, it is submitted that Wheeldon would lead the skilled addressee to an Understanding that application of a β_3-adrenoreceptor agonist to treat heart failure or myocardial hypertrophy is inappropriate. Thus a skilled person would not consider Wheeldon relevant to the treatment of heart failure or myocardial hypertrophy. Furthermore, in view of the comments above in relation to Carson, the Applicants contend that a skilled person would not be motivated to combine the teachings of Wheeldon and Carson to arrive at claims 3-6 and 9-12.

Claims 13 and 14

The Examiner is of the opinion that claims 13 and 14 are obvious in light of Carson and Wheeldon. and furthermore, in conjunction with Cecil (Cecil, Textbook of Medicine). In relation to claim 13, the Examiner is of the opinion that Cecil addresses the further limitations of claim 13 by teaching a variety of approaches to aid in the treatment of heart failure. In particular, the Examiner notes that Cecil teaches that for patients with "life threatening heart failure" (i.e. acute heart failure) the principle objectives are to first stabilize the circulation and maintain organ function.

Furthermore. the Examiner is of the opinion that Cecil teaches the use of ACE inhibitors in mild, moderate and severe heart failure to aid stabilization of the disease which represents at least one of the options of claim 14 as currently pending.

Based on those opinions, the Examiner has concluded that a person of ordinary skill in the art would have been motivated to combine the teachings of Cecil with those of Carson and Wheeldon on the basis that Cecil's teaching of the stabilization of individuals before formulating a therapeutic strategy is a fundamental part of advanced heart failure management. Thus, it is alleged by the Examiner that

it would have been obvious for one of skill in the art, at the time the invention was made. to combine the teachings of Wheeldon, Carson and Cecil to arrive at claims 13 and 14 as currently pending.

As above, the Applicants note the claims require β_3-adrenoreceptor stimulation for the treatment of myocardial hypertrophy or heart failure as set out in claim 3 (on which claims 13 and 14 as currently pending are dependent). Furthermore, claims 13 and 14 relate to the addition of known treatments for stabilization of chronic disease rather than stabilization of acute diseases taught by Cecil. Applicants have addressed the combination of Wheeldon and Carson in earlier comments herein, concluding the combination to be inappropriate in the context of the present invention as inter alia Wheeldon teaches away from β_3-adrenoreceptor activation as a therapeutic intervention for heart failure or myocardial hypertrophy.

Accordingly, it is submitted that the claims under consideration all meet the requirements of 35 USC 103. It is therefore submitted that this application is in order for allowance and an early action to this end is respectfully solicited..

Respectfully submitted,

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